REMARKS

After entry of this Amendment, claims 14, 16-20, 23-29, 31-32 and 35-37 will be pending and under consideration in this application.

Claims 14, 16, 19-20, 23-29 and 31-32 have been amended. Claims 35-41 have been added. Support for the claim amendments and for the new claims can be found throughout the specification. (The specific support for the claim amendments and new claims will be discussed below.) Applicants respectfully submit that none of the claim amendments add new matter to the application.

Claims 1, 3-4, 7-9 and 12-13 have been cancelled without prejudice. Applicants reserve the right to file an application which claims priority to the instant application and contains the subject matter of the cancelled claims.

Indefiniteness Rejections under 35 U.S.C. §112, ¶2

The Examiner has rejected claims 1, 3, 4, 7-9, 12-14, 16-20, 23-29, 31 and 32 under 35 U.S.C. §112, ¶2, as being indefinite due to their recitation of M64347_at. The Examiner states that M64347_at is a GenBank Accession No. and therefore an object which is variable.

Claims 1, 3-4, 7- 9 12 and 13 have been cancelled and, therefore, the rejection with respect to these claims has been obviated.

Applicants respectfully traverse the rejection with respect to claims 14, 16-20, 23-29, 31 and 32, which have been amended to refer to an informative gene comprising certain nucleotides of GenBank Accession No. M64347. Support for this amendment can be found at in the specification which discloses that the Affymetrix "HuGeneFL array" was used, and that M64347_at marker was upregulated. *See* Amendments to the Specification submitted in July 30, 2003, under the heading "Microarray hybridization" and Table 1. As indicated in the Affymetrix website (Exhibit A), M64347_at refers to a set of probes which detect nucleotides 3336-3720 of GenBank Accession No. M64347.

Applicants submit that reference to a GenBank Accession No. does not render the claims indefinite. A person of ordinary skill in the art would be able to determine the nucleotide sequence of a gene by reference to its GenBank Accession No. Further, while a GenBank

Accession No. can be revised, a person of ordinary skill in the art would be to identify any revisions made to a sequence over time. Attached as Exhibit B is print-out from the National Center for Biotechnology Information ("NCBI") website which summarizes their policy with respect to sequences revisions (*see* page 1 of the Exhibit), and states that a person reviewing the records for a particular GenBank Accession No. would be able to determine whether a particular sequence has been revised and would be able to access previous versions of the sequence (*see* page 3 of the Exhibit).

Furthermore, a search of the United States Patent and Trademarks Office ("USPTO") granted patents database reveals that the USPTO has granted patents containing claims which recite sequences by references to their GenBank Accession Nos.[1] Thus, Applicants respectfully request that the Examiner withdraw this rejection.

The Examiner has also rejected claims 12-13, 24-25, 28 and 29 for referring to Table 1 and Tables 2-6. Further, the Examiner states that the reference to the genes in Tables 1-6 by reference to their GenBank Accession Nos. renders the claims indefinite.

Claims 12 and 13 have been cancelled and, therefore, the rejection with respect to these claims has been obviated.

Claims 24-25, 28 and 29 have been amended to replace the reference to the Tables with reference to the GenBank Accession Nos. for the genes disclosed in the Table. Support for this amendment can be found at Tables 1 and 6. Table 1 lists the genes by reference to the probes used to detect the genes disclosed in Table 1, which correlate to the GenBank Accession Nos. for the genes disclosed in the Table 1. Exhibit C provides information obtained from the Affymetrix website which shows such correlation. Note that Exhibit C does not provide the information for all of the probes disclosed in Table 1 since the purpose of the exhibit is to demonstrate that the reference to the probes in Table 1 correlates with the GenBank Accession Nos. of the genes disclosed in Table 1.

Applicants traverse the Examiner's statement that references to GenBank Accession Nos. render the claims indefinite for the reasons discussed above. Accordingly, Applicants

[1] The query used was: "GenBank Accession Number" or "GenBank Accession No." in claims. This search resulted in 18 hits. Among the relevant hits were: U.S. Patent Nos. 6,667,065, 6,627,193, 6,468,773, and others.

respectfully submit that the scope of claims 24-25, 28 and 29 is definite, and request the Examiner to withdraw this rejection.

Applicants note that claims 40 and 41 have been added. Support for the claims can be found throughout the specification, particularly at Tables 1 and 6. Applicants respectfully submit that claims 40 and 41 are definite.

The Examiner has rejected claim 1 as indefinite "for failing to [show the] how the expression profile is correlated with a specific brain tumor type." Further, the Examiner states that "the metes and bounds of two or more informative genes beyond the M64347" is unclear. Claim 1 has been cancelled and, therefore, this rejection has been obviated.

The Examiner has rejected claims 8, 9, 19 and 20 as indefinite because they "lack active method steps, as the recitation of 'utilizing' does not constitute a specific method step."

Claims 8 and 9 have been cancelled and, therefore, the rejection with respect to these claims has been obviated. Applicants respectfully traverse this rejection with respect to claims 19 and 20. Applicants submit that the recitation of "utilizing" in claims 19 and 20 is not intended to be a further method step. Instead the recitation of utilizing provides a further definition of how to determine a gene expression profile. Applicants have amended the claims to improve their form and clarify this point. Accordingly, Applicants respectfully request that the Examiner withdraw this rejection.

The Examiner has rejected claim 14 as indefinite because the use of the term "the sample" lacks antecedent basis. Claim 14 as amended refers to "the brain tumor" rather than "the sample." This amendment renders the rejection moot.

The Examiner has rejected claim 23 as indefinite for its recitation of "survival after treatment" as the predicted treatment outcome. Applicants have amended claim 23 to require the predicted treatment outcome to be a good prognosis of survival after treatment or treatment failure. Support for amended claim 23 can be found at page 9, lines 23-26 of the Substitute Specification. This amendment renders the rejection moot.

The Examiner has rejected claims 26 and 27 as indefinite because of their recitation of: "informative genes", "magnitude", "class distinction", "winning", and "summing the votes", "the sample to be tested", "first class" and "second class". (*See* Office Action, pages 3-4.) More specifically, with respect to claim 26, the Examiner states that "it is unclear how the 'magnitude'

of the vote is to be determined because 'depending on the expression level of the gene' does not accurately define the mathematical relationship between the gene expression and the magnitude of the vote" (Office Action, page 3).

In response to the Examiner's rejections of claims 26 and 27, Applicants traverse in part and amend in part. Applicants have amended these claims to improve their form and to more clearly define the claimed invention. Applicants respectfully submit that the amended claims would be considered definite by a person having ordinary skill in the art.

The claims as amended require calculating the weighted vote of each informative gene. According to the specification, "informative genes" refers to "genes whose expression correlates with a particular phenotype." (*See* Substitute Specification, page 8, lines 23-25 and page 9, lines 13-16.) Thus, with respect to claims 26 and 27, an informative gene is one which correlates with treatment outcome.

Further, the claims have been amended to clarify "class distinction", "first class" and "second class". Applicants respectfully submit that based on the information disclosed in the specification and the knowledge in the art, a person of skill in the art at the time the application was filed would be able to calculate the weighted vote for an informative gene, and to sum up the votes to determine a winning class as required by claims 21 and 22. The weighted voting algorithm was well known in the art at the time the application was filed as evidenced by the fact that the specification cites to three references which use this method. *See* Substitute Specification, page 32, lines 27-28 and Amendments to the Specification submitted in July 30, 2003, under the heading "Weighted Voting", citing to: U.S. Application No. 09/544,627 (now issued as U.S. Patent No. 6,647,341), Golub 1999, and Slonim 2000.

Finally, the Examiner states that claims 26 and 27 are vague and indefinite because it is unclear if the level of gene expression used in the computation is a normalized or non-normalized level. Applicants respectfully traverse. Applicants submit that it is irrelevant to the claimed methods, and that a person of skill in the art would know whether the gene expression level should be normalized or non-normalized in a particular instance. Accordingly, Applicants respectfully request that the Examiner withdraw this rejection.

Enablement Rejections under 35 U.S.C. §112, ¶1

The Examiner has rejected claims 1, 3, 4, 7-9, 12-14, 16-20 and 23-29 for lack of enablement.

Applicants have cancelled claims 1, 3, 4, 7-9, 12 and 13, directed to methods of classifying a brain tumor. Therefore, the Examiner's rejections with respect to these claims have been obviated.

Applicants traverse the Examiner's enablement rejection with respect to claims 14, 16-20 and 23-29, directed to methods of predicting the efficacy of treating a brain tumor, methods for predicting a treatment outcome of a patient with a brain tumor, methods for evaluating drug candidates for their effectiveness in treating a brain tumor or methods for monitoring the efficacy of a brain tumor.

According to the Examiner, "[t]here are no teachings in the specification to correlate a value which is several standard deviations from the mean with a method of predicting the efficacy of a brain tumor. More specifically, the Examiner states that: (1) the specification does not teach whether the expression of M64347 as shown in Figure 3C was obtained from the brain tumor before treatment or after treatment, (2) it is unclear if the lowered expression of M64347 is indicative or predictive of treatment failure or a treatment success as the title of Figure 3C is "Markers of Treatment Failure" but the heading of Table 1 is "Markers Downregulated with Low Risk" and (3) the specification does not define how the C1 or C0 groups were differentiated and does not teach what constitutes a treatment failure or success in terms of disease free survival or length of survival.

As mentioned above, Applicants traverse. First, the specification teaches that expression of M64347 as shown in Figure 3C was obtained from the brain tumor before treatment. *See* Substitute Specification, page 40, line 28 to page 41, line 2.

Second, the specification (Table 1, Table 6 and Figure 3C) shows that the upregulation of M64347 is correlated with a "high risk class" of individuals (*e.g.*, a class of individuals with poor prognosis for survival after treatment). *See* Substitute Specification, page 9, lines 13-16 stating that "a sample can be classified as belonging to a high risk class (e.g., a class with poor prognosis for survival after treatment) or a low risk class (e.g., a class with good prognosis for survival after treatment)." Thus, the heading of Table 1 – "Markers Upregulated in High Risk,

Downregulated in low Risk" – is not inconsistent with the heading of Figure 3C – "Markers of Treatment Failure" – as it appears to be suggested by the Examiner.

Third, the specification describes that in Figure 3 C0 and C1 correspond to two unsupervised SOM-derived clusters, and that Class C1 tumors are notable for their high ribosomal content. *See* Substitute Specification, page 7, lines 2-4. The specification further states that the C0 and C1 groups were not correlated with patient survival. *See* Substitute Specification, page 41, lines 13-17.

Finally, the specification teaches what constitutes treatment failure or success in terms of disease free survival or length of survival. The specification states that they differentiated "patients who are alive following treatment ('survivors') compared to those [patients] who succumbed to their disease ('failures'; minimum follow-up 24 months for surviving patients; overall median 41.5 months)." *See* Substitute Specification page 41, lines 17-21.

The Examiner also states that "[t]here is no guidance for a specific polynucleotide probe and hybridization conditions to be used in the determination of an expression profile for . . . the method of predicting the efficacy of treatment." The Examiner noted there are different isoforms of FGFR3, the gene encoded by M64347, and stated that a probe to this gene could hybridize to any number of the polymorphic gene products or alleles. The Examiner concluded that the "specification provides no teachings as to the exact nature of the probe used for the expression profile, thus it cannot be construed from the specification which polymorphic variants, splice variants or alleles are integral to the claimed invention."

Applicants note that not all of the claims recite the use of a probe and/or require the use of hybridization condition to determine an expression profile. In any case, Applicants respectfully traverse the Examiner's rejection to the extent that certain claims require the use of a specific polynucleotide probe and hybridization conditions.

Contrary to the Examiner's assertion, the specification teaches the exact nature of the probes used to determine the expression profiles for the classification of a brain tumor, or the method of predicting the efficacy of treatment. The specification states that they used Affymetrix's HuGeneFL array. (*See* Amendments to the Specification submitted in July 30, 2003, under the heading "Microarray hybridization.") Based on this disclosure, a person of skill in the art would have been able to identify the probes present in the array and used in the

specification to determine the expression profiles for the method of predicting the efficacy of treating a brain tumor.

More specifically, based on the disclosure, a person skilled in the art would have been able to determine the specific probe used to determine the expression profile of M64347, and the other informative genes disclosed in the specification. The claims have been amended to recite an informative gene comprising nucleotides 3336-3720 of GenBank Accession No. M64347, which are the nucleotide sequences in Affymetrix's HuGeneFL array. *See* Exhibit A (obtained from Affymetrix's website). Thus, Applicants submit that the claims, as amended, are enabled with respect to the probes which can be used to practice the methods of the claimed invention.

Applicants respectfully submit that, in view of the specification, which teaches that the expression profile of an informative gene which hybridizes to nucleotides 3336 to 3720 of GenBank Accession No. M64347 correlates with efficacy of treating a brain tumor, the fact that there are different allelic variants or isoforms of the gene encoded by GenBank Accession No. M64347 is irrelevant.

Applicants respectfully submit that a person of ordinary skill in the art would know what hybridization conditions should be employed to determine the expression profile of the informative genes of the claims. Moreover, the specification teaches the hybridization conditions used in the experiments disclosed in the specification. (*See* Amendments to the Specification submitted in July 30, 2003, under the heading "Microarray hybridization.") Thus, Applicants submit that the claims are enabled with respect to the hybridization conditions useful in practicing the methods of the claimed invention.

With respect to claims 26-29, the Examiner states that "the specification does not define the parameters needed to calculated weighted vote for M64347." Applicants respectfully traverse. As discussed above, based on the information disclosed in the specification, a person of skill in the art would know how to determine weighted vote as recited in the claims without undue experimentation as evidenced by the fact that the specification refers to a patent application (U.S. Application No. 09/544,627, now issued as U.S. Patent No. 6,647,341) and two papers (Golub 1999 and Slonim 2000) that disclose the use of this weighted voting algorithm before the instant application was filed. (*See* Substitute Specification, page 32, lines 27-28 and

Amendments to the Specification submitted in July 30, 2003, under the heading "Weighted Voting.")

The Examiner states that "Applicants arguments regarding the teachings of Golub et al. for methods of determining class and subclass as set forth in U.S. application No. 09/544,627 are unpersuasive" because the instant application could issue before the referenced application. (*See* Office Action, page 7.) Applicants note that the referenced application has now issued as U.S. Patent No. 6,647,341. Applicants have amended the application accordingly.

In view of the arguments presented above, Applicants respectfully request that the Examiner withdraw the enablement rejections.

Obviousness Rejections

The Examiner has rejected claims 31 and 32 under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 6,500,938 ("*Au-Young*") in view of Abbass et al., 1997, *J. Clin. Endocrinol. Metab.*, 82:1160-1166) ("*Abbass*"), or over U.S. Patent No. 6,218,122 ("*Friend*") in view of *Abbass*.

The Examiner alleges that *Au-Young* teaches methods of monitoring the progression of a disease or the efficacy of a treatment comprising detecting an expression profile by means of a micro array. The Examiner alleges that *Friend* teaches methods for detecting changes in a biological state of a subject which are correlated to one or more disease states and methods for monitoring the efficacies of a therapy comprising the determination of an expression profile from said cells in a patient. However, as admitted by the Examiner, neither *Au-Young* nor *Friend* teaches the expression profile of M64347 or the FGFR3 encoded thereby.

The Examiner alleges that *Abbass* teaches "that the expression of the mRNA encoding the secreted form of FGFR3, which would be expressed from the M64347_at gene, is correlated with pituitary adenomas." Further, as admitted by the Examiner, *Abbass* does not teach a correlation between the expression profile of FGFR3 and tumor type, size or aggressiveness. (*See* 12/31/03 Office Action, page 5.)

It is respectfully pointed out to the Examiner that a proper rejection based on 35 U.S.C. §103 that relies on a combination of prior art references requires a teaching, suggestion, or

motivation to combine the teachings of the references; a reasonable expectation of success founded in the cited art of producing the claimed invention; and that such proper combination teaches or suggests all elements of the claimed invention. Applicants respectfully traverse the obviousness rejections for failing to meet all of these requirements for the reasons provided below.

Claims 31 and 32, as amended, recite methods for evaluating drug candidates for their effectiveness in treating brain tumors or methods for monitoring the efficacy of a brain tumor treatment, wherein the brain tumor is selected form the group consisting of mellanoblastomas, glioblastomas, rhabdoid tumors, primitive neuroectodermal tumors, and pineoblastomas. Support for this amendment, and for newly added claims 35-39, can be found throughout the specification. *See, e.g,,* Substitute Specification, page 3, lines 1-2.

Applicants respectfully submit that there is no motivation to combine the references cited by the Examiner to reach the invention of amended claims 31 and 32. The Examiner states that "one of ordinary skill in the art would have been motivated to [combine the references] with a reasonable expectation of success by the teachings of Abbass et al. on the unique expression of the secretable form of FGFR3 mRNA in pituitary adenomas versus the lack of expression of the secretable form of this receptor in normal pituitary." However, none of the references teach the correlation between the gene expression profile of M64347 and effectiveness in treating a brain tumor selected from the group consisting of mellanoblastomas, glioblastomas, rhabdoid tumors, primitive neuroectodermal tumors, and pineoblastomas, or monitoring the efficacy of a treatment for any of the mentioned brain tumors. Therefore, there would be no motivation to combine the references as argued by the Examiner.

Further, even if the references were to be combined as suggested by the Examiner, the combination of references would not teach or suggest the inventions of claims 31 and 32. Rather, the combination of the references would <u>at best</u> teach the use of M64347 to evaluate drug candidates for their effectiveness in treating a pituitary adenoma, or to monitor the efficacy of a pituitary adenoma treatment. Nothing in the cited references suggests or discloses the use of M64347 to evaluate drug or monitor the efficacy of a drug to treat the brain tumors of the claims. Moreover, even if the references were combined, there would be no reasonable expectation of success. Accordingly, Applicants respectfully request that the Examiner withdraw the obviousness rejections.

Conclusion

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 18-1945, under Order No. WIBL-P01-561 from which the undersigned is authorized to draw.

Dated: March 31, 2004

Respectfully submitted,

By _____

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